



## Five-year outcome in immune-mediated scleritis

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# Five-year outcome in immune-mediated scleritis

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## Abstract

**Background** Immune-mediated scleritis is a rare condition, and the information on the clinical course and complications is scarce. The aim of this study was to identify prognostic factors, complications, and therapeutic effects in patients with immune-mediated scleritis.

**Methods** Patients with diagnosis of scleritis and a follow-up time of 5 years were identified. Systemic disease, laboratory investigations, type of scleritis, disease activity, therapy, and complications were recorded. The study design was a retrospective, non-comparative, interventional case series.

**Results** Systemic disease was identified in 15 (37 %) patients at presentation and in 18 (45 %) after 5 years. Rheumatoid arthritis (15 %), granulomatosis with polyangiitis (7.5 %), and polychondritis (7.5 %) were the most predominant disorders. Persistent scleritis (>5 years) was associated with systemic disease (66 vs. 6 %;  $p<0.05$ ) and positive auto-antibodies (48 vs. 23 %;  $p=0.18$ ). Control of ocular inflammation was achieved in 38 of 40 (95 %). Prednisone (14 patients) and/or methotrexate (8) were the predominant drugs to control persistent disease. Complications included interstitial keratitis (2), inflammatory astigmatism (2), corneal melt (3), macular edema (6), and severe systemic disease (5).

**Conclusion** The presence of systemic disease and positive auto-antibodies are associated with persistent scleritis. Immunosuppressive agents allow control of scleritis, but may contribute to severe systemic complications.

**Keywords** Scleritis · Cornea · Keratitis · Outcome · Inflammation · Immunopressive therapy · Steroids

## Introduction

Scleritis often occurs as a chronic inflammatory process. Although in some instances it may be caused directly by an infective agent, the vast majority of cases present as an immune-mediated disorder [1–3]. Immune-mediated scleritis may be associated with systemic disease. Usually systemic therapy is required to control inflammation. Morphologic criteria are used to classify scleral inflammation clinically into anterior and posterior types [3]. Anterior scleritis is subclassified into diffuse, nodular, necrotising with inflammation, and necrotising without inflammation (scleromalacia).

Little information on the clinical course and complications of scleritis is available [4–7]. This study aims to gain knowledge on the long-term outcome of scleritis, and to identify prognostic factors. This was done by studying systemic disease and laboratory findings, and by the assessment of complications and therapeutic effects.

## Patients and methods

In 2010 we reviewed the records of more than 100 patients who were referred to our institution with the diagnosis "scleral inflammation". Forty patients and 56 affected eyes with diagnosis of immune-mediated scleritis and the possibility to be followed by our team for the next 5 years were identified and investigated. After having obtained informed consent, these patients were included in the study. The demographic data are shown in Table 1. Immune-mediated scleritis was diagnosed on clinical grounds (constant and nocturnal pain with spreading to the periorbital region, scleral edema, tenderness of the

This work has not previously been presented.

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**Table 1** Demographic data

Age at presentation (median)	51 years (range 31–74)
Females/males	65 %/35 %
Relative and absolute number of patients at follow-up (months)	100 % (40) at 12 95 % (38) at 36 95 % (38) at 60 55 % (18) at 120 months
Deceased (relative and absolute number of cases at follow-up in months)	5 % (2) 12–60 17.5 % (7) 61–120

globe, presence of nodules, or signs of scleral necrosis), and was supported in two cases by tissue examination (absence of infective agents). Patients with superficial inflammation (rather episcleritis than scleritis), infectious scleritis, neoplastic lesions, and/or incomplete data were excluded. A standardised protocol was used to record systemic disease, laboratory investigations, type of scleritis, disease activity, therapy, and complications (Table 2). The duration of scleritis was determined as absence of clinical inflammation for more than 6 months after stopping therapy (local and systemic).

For the treatment of scleritis, an anti-inflammatory strategy was applied as published elsewhere [8]. For non-necrotising scleritis oral nonsteroidal anti-inflammatory drugs such as flurbiprofen (100–300 mg/24 h), sometimes in combination with steroids, were used to induce remission. For consolidation, methotrexate, azathioprine, anti-TNF-alpha blockers or cyclosporine were applied. Necrotising scleritis was treated with high-dose oral prednisone or intravenous methylprednisolone in combination with cyclophosphamide. Cyclophosphamide was given parenterally in an initial phase, later per os. Posterior scleritis was treated in this series solely with oral prednisone. All medication was given according to the guidelines of the Rheumatology Department, University Hospital of Zürich (Head Prof. Beat Michel) and supervised by experienced rheumatologists. Successful medical control of disease was defined as absence of symptoms, clinical inflammation and, in necrotising disease, halt of further tissue destruction.

The contingency table (see Table 6) was analysed using Fisher's exact test. Patients with persistent scleritis (more than

**Table 3** Association of scleritis with systemic disease

At first presentation: 37.5 % (15)	
During the further course: 45 % (18)	
Rheumatoid arthritis	15 % (6)
Polychondritis	7.5 % (3)
Granulomatosis with polyangiitis (formerly Wegener's granulomatosis)	7.5 % (3)
Polyarteritis nodosa	2.5 % (1)
HLA-B27 positive (ankylosing) spondylitis	2.5 % (1)
HLA-B27 negative spondylitis	2.5 % (1)
Scleroderma	2.5 % (1)
Colitis ulcerosa	2.5 % (1)
Cogan's syndrome	2.5 % (1)

5 years of ongoing scleral inflammation) were compared with patients who showed a shorter course of scleral inflammation.

## Results

The median age at first presentation was 51 years, and 65 % were females. In 37.5 % (15 patients), a systemic disorder was already known at presentation; in the further course the figure raised to 45 % (18). Rheumatoid arthritis was the most frequent systemic disease (15 % or six patients), followed by polychondritis in three, and granulomatosis with polyangiitis (GPA) in three patients (Table 3). The type of scleritis at presentation is shown in Table 4: Non-necrotising anterior scleritis was the most frequent type (77.5 %, 31 eyes). Necrotising anterior scleritis was seen in five and posterior inflammation in six eyes. Two eyes had both inflammation of the anterior and posterior segments. In 26 out of 40 patients, the scleritis stayed unilateral. In four patients, however, scleral inflammation became bilateral (Table 5). During follow-up, the type of scleritis changed in four patients; one patient who had initially presented with anterior disease developed posterior scleritis. One patient with initial posterior disease

**Table 2** Protocol for the investigation of scleritis patients

Systemic disease
Laboratory investigations (serum rheumatoid factor, ANA, ANCA)
Type of scleritis
Disease activity at presentation, 12, 36, 60, and 120 months
Therapy
Complications

**Table 4** Type of scleritis at presentation

		Unilateral	Bilateral
Diffuse/nodular	77.5 % (31)	45 % (18)	32.5 % (13)
Necrotising	12.5 % (5)	12.5 % (5)	0
with inflammation	7.5 % (3)	7.5 % (3)	
without inflammation	5 % (2)	5 % (2)	
Posterior	15 % (6)	7.5 % (3)	7.5 % (3)
Total <sup>a</sup>		62 % (26) <sup>a</sup>	38 % (16) <sup>a</sup>

<sup>a</sup> Two eyes with anterior and posterior inflammation

**Table 5** Scleritis course (0–60 months)

Unilateral → bilateral	4
Changing type of scleritis	4
Anterior → Posterior	1
Posterior → Anterior	1
Nodular/diffuse → Necrotising	2

developed non-necrotising anterior scleritis 2 years later. Two patients with non-necrotising inflammation at first visit developed ischemic areas, thus necrotising scleritis (Fig. 1).

In 21 out of 40 patients (52 %) scleral inflammation lasted more than 5 years. This persistent scleritis (more than 5 years ongoing scleral inflammation) was associated with systemic disease (14/21 in comparison to 1/17 patients with shorter inflammation episodes). This association was statistically significant when analysed by Fisher's exact test. The presence of positive circulating antibodies (10/21 versus 4/17) showed a trend to favour persistent inflammation. This is shown in Table 6.

Information on the medical control of scleral inflammation is given in Tables 7 and 8. Control of scleritis was achieved in 38 out of 40 patients. In two patients with necrotising scleritis, the loss of scleral tissue could not be halted. One of these patients, a 75-year-old male, developed stomach carcinoma and therapy with cyclophosphamide was subsequently stopped. This patient died 18 months after first presentation. The other patient, a 39-year-old female with severe rheumatoid arthritis, developed ongoing scleromalacia despite immunosuppression with oral steroids, cyclophosphamide and TNF-alpha-blockade (Figs. 2 and 3).

The complications of scleral disease are listed in Table 9. Corneal complications included interstitial keratitis (two eyes), peripheral corneal melts (three eyes) and scleritis-induced astigmatism (two eyes) (Fig. 4, Table 10). Six patients developed cystoid macular edema. In two patients the scleritis had led to persistent structural damages and functional loss (long-standing retinal detachments without light perception). Several patients developed severe systemic disease: myocardial



**Fig. 1** patient with non-necrotising at first visit developed ischemic areas, thus necrotising scleritis

**Table 6** Duration of scleritis

	<5 years	>5 years	<i>p</i> value*
Percentage (effective)	43 % (17)	52.5 % (21)	
Systemic disease	1/17	14/21	< 0.05
Autoantibodies	4/17	10/21	0.18
Serum rheumatoid factor (ELISA >25mu/ml)	2	7	
ANA (Titer, >1:10)	2	5	
ANCA (Titer, >1:10)	0	3	

No clinical inflammation for >6 months after stopping therapy (local and systemic)

\**p* by Fisher's exact test

infarction at age 44 and IgA-nephropathy, pericarditis with valvular and coronary heart disease (possibly associated with the polyarteritis nodosa), and two patients died within the 5-year follow-up period (Table 11).

## Discussion

Information on the outcome of scleritis is scarce. To date, there are case reports and the Moorfields, Boston, and Baltimore cohorts [1, 3, 6] that help to understand the nature of scleral inflammation. Our study sets the focus on the long-term course of scleritis and, in this way, teaches us about the outcome of immune-mediated scleritis.

Scleritis is a potentially long-lasting problem. Fifty-two percent of our patients showed a disease duration of more than 5 years. Although this figure may be biased by the fact that we see patients as tertiary referrals, we were surprised by this high number. An underlying systemic disease and positive autoantibodies were identified as risk factors for such a long disease duration.

Melts, interstitial keratitis, and peripheral ulcerative keratitis are well known corneal complications of scleritis [4–7]. Inflammatory astigmatism due to scleritis was previously described [9, 10], but none of those patients had such a high cylinder measurement as our patient with 8.5 diopters (Table 10). A second patient of our series had a cylinder measurement of 2.5 diopters. In both patients it was reversible after remission of scleritis. We feel that it is the increase in

**Table 7** Medical control of disease activity

	Yes	No
Control of inflammation	38	2 <sup>a</sup>

No discomfort, no further destruction

<sup>a</sup> Ongoing destruction in the two patients with scleromalacia



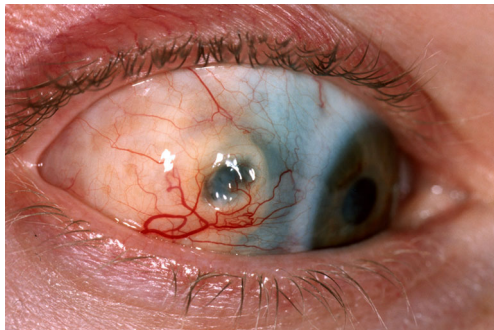
**Table 8** Systemic medication in 40 scleritis patients

	0–1 months	12 months	36 months
NSAID	20	10	3
Prednisone	21	22	14
Cyclophosphamide	5	3	—
Methotrexate	5	6	8
Azathioprine	2	1	1
Anti-TNF-alpha			
<i>Infliximab (Remicade®)</i>			1
<i>Adalimumab (Humira®)</i>		1	1
Cyclosporine A	1	1	

**Table 9** Complications (months 0–60)

Interstitial keratitis	2
Scleritis-induced astigmatism	2
Peripheral corneal melt	3
Cystoid macular edema	6
Persistent structural damage → <i>enucleation</i>	2
Severe systemic disease	5
Myocardial infarction at age 44, IgA-nephropathy	1
Pericarditis, valvular/coronary heart disease	1
Deceased (patients #5 and #6)*	2

\*For details of these patients see Table 11



**Fig. 2** Scleromalacia in a 39-year-old female with severe rheumatoid arthritis. There is progressive scleral destruction despite immunosuppression with oral steroids, cyclophosphamide, and TNF-alpha blockade



**Fig. 4** A 73-year-old female who developed anterior and posterior non-necrotizing scleritis. The scleral nodule in the upper and nasal quadrants resulted in a corneal astigmatism of  $-8.50$  in  $117^\circ$ . The course of the corneal curvature is shown in Table 10



**Fig. 3** The same eye as in Fig. 2. The progression over a period of 5 years is obvious

**Table 10** Corneal astigmatism before and after onset of anterior non-necrotizing scleritis which responded to treatment with oral steroids. The affected eye is shown in Fig. 4

Follow-up time	Autorefracton (NIDEK ARK-700A)
Pre-inflammatory refraction	$-3.50 -1.25 110^\circ$
Day 1	<sup>a</sup> $-8.50 117^\circ$
Day 14	$-1.00 -6.00 110^\circ$
Day 28	$-1.75 -4.50 116^\circ$
Day 42	$-1.50 -4.25 113^\circ$
Day 90	$-0.75 -3.75 111^\circ$
Day 120	$-1.00 -3.75 111^\circ$

<sup>a</sup> Sphere not measurable

**Table 11** Deaths (0–120 months)

Patient	Cause of death	Type and duration of scleritis (months)	Systemic inflammatory disease	Systemic medication
C.A., ♂, age 76 years, # 5	Stomach carcinoma	Necrotising, 9		Steroids, cyclophosphamide
E.M., ♀, age 68 years, #6	Not known	Anterior and posterior, > 60		Steroids, azathioprine
E.W., ♂, age 72 years, # 7	Aplastic anemia	Necrotising, 38	Rheumatoid arthritis	Steroids, methotrexate, cyclophosphamide, later azathioprine
H.H.R., ♂, age 45 years, # 12	Sepsis (immunosuppression?)	Diffuse anterior, 120	Polychondritis	Steroids, infliximab
K. H., ♂, age 70 years, #13	Renal failure	Diffuse anterior, 21	Polychondritis	Steroids, cyclosporine
L. M., ♀, age 80 years, # 17	Heart failure	Diffuse anterior, 15	Cogan's syndrome	Steroids, cyclophosphamide
S.F., ♂, age 79 years, # 26	Aortic aneurysm	Necrotising, 9		Steroids, cyclophosphamide

volume of the inflamed sclera that leads to changes of scleral rigidity with subsequent instability of limbal contour and corneal steepening in the affected quadrant.

Macular edema was observed in 11 % of our patients. When detected at an early stage it was fully reversible after high-dose oral steroids. One of our patients presented with posterior scleritis only and developed anterior scleritis years later in the same eye, and three other eyes changed the type of scleritis (Table 5). This is in contrast to Tuft's study [11] who found that the majority of patients remain in the same clinical category. It seems that a change in the scleritis pattern is not unusual when patients are available for long-term follow-up.

The evaluation of the best medication for the treatment of scleritis was beyond the scope of this study. With the correct application of traditional and new generation immunosuppressive agents, preferably in collaboration with a rheumatologist, disease control is possible in most cases. In our series, remission was achieved in 95 %. In one patient with long-standing rheumatoid arthritis and scleromalacia (Figs. 2 and 3), tissue loss could not be halted despite application of TNF-alpha blockers and, at a later stage, cyclophosphamide in combination with oral steroids. This demonstrates again that this vasculitic complication is particularly difficult to tackle [1, 6, 7].

Our patients showed a considerable morbidity and a high number of lethal complications. Five percent of our patients died within 5 years and 17.5 % within 10 years of follow-up time. Three of the deaths were older than 75 years and presumably died of natural causes. Of concern are the two patients who died with aplastic anemia and septicemia. This demonstrates that the immunosuppressive therapies have the potential to cause lethal complications, although the systemic disease itself may be life-threatening [1, 2]. New agents allow

control of scleritis, but may also contribute to systemic complications.

**Proprietary interest** None.

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